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GUEST EDITORIAL

Should Irradiation Replace Dissection for Patients with Breast Cancer with Clinically Negative Axillary Lymph Nodes?

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INTRODUCTION

The use of axillary irradiation (AxRT) and axillary dissection (AxD) for patients with early-stage invasive breast cancer with clinically negative axillary nodes must be placed within the context of the overall goals of treatment. One treatment goal is to destroy occult distant metastases present at the time of diagnosis through the use of systemic therapy. Another goal is to achieve local–regional tumor control to prevent morbidity and possibly improve the chance of cure. (I have discussed the evidence that such treatment increases survival rates elsewhere and hence will not review it here [1,2].)

Sentinal node biopsy (SNB) is increasingly used to determine whether patients have pathologic nodal involvement. However, suppose that knowing the exact number of involved nodes is not important to select the type of systemic therapy used. Alternatively, suppose some patients will receive the same systemic therapy regardless of the pathologic axillary nodal status; hence, even SNB would not be indicated (e.g., an elderly patient with a 2-cm primary tumor who will receive tamoxifen but not chemotherapy). In either situation, can the goal of axillary nodal control be achieved by AxRT—or even radiotherapy directed at only the breast (BrRT)—and by AxD?

This editorial investigates these questions. It is generally agreed that patients with clinically suspicious axillary nodes should undergo AxD; hence, their management will not be addressed. The risk of axillary failure in the absence of any treatment by surgery or radiotherapy has been discussed elsewhere [1], as have the toxicities of AxRT and AxD [1] and the effectiveness of salvage therapies for axillary recurrences [3]. Hence, these topics are not discussed in this editorial.

IS FURTHER SPECIFIC AXILLARY TREATMENT NEEDED FOR PATIENTS WITH A NEGATIVE SNB?

Overview

The decision as to whether further axillary staging or treatment is necessary in patients with a negative SNB depends on several factors: the accuracy of this procedure in assessing nodal status (specifically, its false-negative rate); the risk of axillary recurrence in patients with a negative SNB; and the effectiveness of AxD, AxRT, or (in patients treated with breast-conserving surgery) BrRT in eradicating such disease. These topics are reviewed.

False-Negative Rates of SNB

The reported rate of false-negative SNB ranges from 0% to 12% [4,5]. This variability is seen even in reports from major centers or studies with detailed quality-assurance protocols, for example, 7% in a series from the European Institute of Oncology in Milan, Italy [6]; 4% in the multicenter validation trial of Krag et al. [7]; 1% (1/186) for the University of South Florida group in Tampa, Florida [8]; and 2% (1/60) for the John Wayne Cancer Institute group in Santa Monica, California [9].

Some of these discrepancies arise from differences in the techniques used to examine the recovered sentinal nodes and in how "positive" nodes are defined. For ex-

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ample, the latter two series noted above routinely used immunohistochemical staining. In the John Wayne Cancer Institute series, this resulted in 14% (10/70) of patients with negative sentinal nodes on standard light microscopic examination with hematoxylin–eosin being relabeled as having positive sentinal nodes [9]. In the University of South Florida series, such upstaging due to immunohistochemical findings occurred in 11% (41/385) of patients [10]. The number of sections of each node examined by light microscopy may also have affected the risk of having a false-negative SNB [11,12]. One study combining 0.25-mm serial sectioning with immunohistochemistry resulted in converting 59% (16/27) of 27 patients with negative SNB on 2-mm serial sectioning with hematoxylin–eosin staining to a positive status [13].

Another variable affecting the rate of false-negative SNB is surgeon experience and skill. There was substantial variability in the false-negative rate from surgeon to surgeon in both the multicenter validation study (0%–29%) [7] and a series from Memorial-Sloan Kettering Cancer Center in New York (8%–33%) [14]. False-negative rates (and failure to find any sentinal nodes) tend to decline with experience. In the Memorial-Sloan Kettering Cancer Center series, the false-negative rate was 11% (5/47) of all cases operated on; however, when each surgeon's first 6 cases were eliminated, the rate dropped to 5%; when each surgeon's first 15 cases were eliminated, the rate dropped to 2% [14].

It is less clear what other factors affect the false-negative rate. In an early report of the experience at Memorial-Sloan Kettering Cancer Center, the accuracy of SNB appeared to decrease as tumor size increased [15]. However, their more recent experience found a false-negative rate of approximately 5%, regardless of tumor size [5]. Other factors that have been thought to raise the risk of having a false-negative SNB include having multicentric disease [16] and prior excisional biopsy [17,18]. However, prior excision did not increase this rate in other series [15,19,20].

Location and Number of Involved Nonsentinal Nodes in Patients with False-Negative SNB

The location in the axilla of involved nonsentinal nodes in patients with a false-negative SNB has been examined only in the European Institute of Oncology series. Nine of 12 patients had involvement of nodes in level I, 2 patients had involvement of levels I and II, and 1 patient had involvement of levels I, II, and III [6]. In that series, 8 of the patients with false-negative SNB had 1 involved nonsentinal node on AxD, 1 patient had 2 positive nodes, 2 patients had 3 positive nodes, and 1 patient had 4 positive nodes [6]. Results were nearly identical in the multicenter trial: 1 positive nonsentinal node in 8 patients, 2 positive nodes in 3 patients, and ≥ 4 positive nodes in 2 patients [7].

Axillary Failure Rates after a Negative SNB or Axillary Sampling

There have been no detailed long-term reports concerning the risk of axillary failure in breast cancer patients with a negative SNB. A brief description of the John Wayne Cancer Institute experience noted that there were no axillary recurrences among patients with a negative SNB who had not undergone subsequent AxD with a minimum 2-year follow-up [21]. However, the number of such patients, the actual length of follow-up, and other details of their tumors and treatment were not described.

The rate of nodal failure following a negative SNB has been reported in several series of patients with melanoma. This rate was 2% (11/572) in the John Wayne Cancer Institute series [22]. However, this rate was 7% (6/89) in a series from the Massachusetts General Hospital in Boston [23]. In a series from the M.D. Anderson Cancer Center in Houston, 3% (7/243) of patients developed an isolated nodal basin failure as the first site of failure [24]. Seven other patients (3%) developed failure in the SNB basin either after development of a local or in-transit recurrence (4 patients) or after development of distant metastases. Of note, specimens from these two latter institutions were processed by using only conventional light microscopy with standard hematoxylin–eosin staining, whereas the John Wayne Cancer Institute has typically also employed immunohistochemistry.

The incidence of axillary failure is generally increased after inadequate axillary surgery [1]. Hence, examination of results in patients treated with such surgery may be useful in setting an upper boundary on the risk of axillary recurrence after a negative SNB.

In a trial performed in Yorkshire, England, surgeons performed either an "axillary sampling" (removing the pectoral nodes and the nodes in proximity to the axillary tail of the breast only) or an "axillary dissection" (removing nodes and fat up to the axillary vein and cleaning the subscapular neurovascular bundle) in addition to total mastectomy [25]. Axillary failure rates among node-negative patients undergoing axillary sampling or complete AxD were 8% and 3%, respectively. In a trial conducted in Edinburgh, Scotland in 1980–1983 in which patients with operable invasive breast cancer were also randomized between axillary sampling and AxD in addition to undergoing total mastectomy, axillary failure rates were 4% (5/115) and 2% (3/123) in patients with negative nodes in the sampling and clearance groups, respectively [26]. However, higher rates of failure were found in two other Scottish series in node-negative patients treated with axillary sampling only (13% [27] and 16% [28]).

Several investigators have examined the risk of axillary failure in relation to the number of lymph nodes recovered from the surgical specimen. A report from

Denmark found that, for patients without pathologic involvement of the recovered nodes, the 5-year actuarial risk of axillary recurrence was 10% when only 1–2 nodes were found in the specimen, 5% if 3–4 nodes were found, and 3% when ≥5 nodes were recovered [29]. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial, failure rates were 21%, 12%, and 0% among patients when 0, 1–5, or ≥6 negative nodes, respectively, were found in the axillary specimen [30].

Treatment of patients with BrRT but not AxRT may decrease the risk of axillary failure after limited AxD. Currently used treatment techniques ordinarily result in the lower portion of the axilla (levels I and part but not always all of level II) being included in the same photon fields as those used to treat the breast or chest wall [31,32]. In a series of patients treated with BrRT at the Joint Center for Radiation Therapy, Boston, 2 of 10 patients had recurrence in the axilla when only 1 node or no nodes were found in the AxD specimen; when 2–3 nodes were found, 0 of 5 patients had recurrence; and when 4–5 nodes were recovered, 0 of 26 patients had relapse in the axilla [33]. Similar data have been reported for patients treated at the University of Pennsylvania [34]. A 1% risk of axillary failure was found in a group of 189 node-negative patients treated in Ashford, England between 1986 and 1994 with axillary sampling and BrRT [35]. No axillary failures were observed (with a short median follow-up of 20 months) among 49 patients who had a negative four-node axillary sampling in conjunction with breast-conserving surgery and BrRT in a series from Harrow, England [36].

Conclusions

The large majority of patients who have a false-negative SNB will likely have only 1–2 involved nonsentinal nodes. These nodes will usually be inside the standard tangential fields used to irradiate the breast. As a result, the risk of clinical axillary node failure in patients with a false-positive SNB treated with breast-conserving surgery and BrRT seems likely to be at most a few percent, quite comparable to the rate after a negative level I/II AxD [1]. Hence, at present, routine AxRT or completion AxD does not appear warranted after a negative SNB. More data on this issue will be gathered by the NSABP trial B-32, in which patients are randomized to either SNB or conventional AxD. Patients in this trial with a negative SNB will not undergo specific axillary treatment.

IS FURTHER SPECIFIC AXILLARY TREATMENT NEEDED FOR PATIENTS WITH A POSITIVE SNB?

Overview

Before decisions are made about whether patients with a positive SNB should undergo AxRT or AxD or whether BrRT only (or no further treatment of even the lower axillary region) might be appropriate, it is important to know four things: What is the chance that tumor-bearing nodes are left in the axilla? In which part of the axilla are the nodes are located? How many of these are there? and What is the risk of recurrence without further specific axillary treatment?

Risk of Involvement of Nonsentinal Nodes in Patients with Positive SNB

The risk of involvement of nonsentinal nodes in patients with a positive SNB has ranged from one-third to two-thirds in reported series (summarized elsewhere [4,5]). However, the correlates of having additional involved nodes have not been analyzed in detail in most studies.

In the John Wayne Cancer Institute series, only the size of the sentinal node metastasis and the size of the primary tumor were statistically significant risk factors in multivariate analysis for involvement of the nonsentinal nodes on completion level I/II AxD [37]. Patients in this series were scored as having a positive SNB when the node was involved either on conventional light-microscopic examination or by immunohistochemistry. The risk of having involved nonsentinal nodes was 7% for 69 patients with micrometastases (≤2 mm) in the sentinal nodes and 55% for 88 patients with macrometastases. Of note, 0 of 33 patients with micrometastases detected only by immunohistochemistry had further axillary involvement as opposed to 14% (5/36) of patients with micrometastases determined by conventional light microscopy. The risk of nonsentinal node involvement also increased with increasing tumor size (0 of 5 patients—4 with micrometastases—with T1a lesions, 13% with T1b lesions, 29% with T1c lesions, 38% with T2 lesions, and 71% with T3 lesions). Among patients with T1b tumors, none (0/10) with micrometastases and 40% (2/5) with macrometastases had nonsentinal node involvement. The percentages of patients with tumors were 6% (2/32) and 50% (17/34) for T1c tumors, 10% (2/20) and 53% (20/38) for T2 tumors, and 33% (1/3) and 82% (9/11) for T3 tumors. (These data were not further subdivided by whether the micrometastases had been found only by immunohistochemistry or by light microscopy also.)

A similar study pooling 60 patients with positive SNB from the Mayo Clinic, Rochester, Minnesota, and the University of Pennsylvania, Philadelphia, also found that primary tumor size and the size of the sentinal node metastasis (micro- vs. macrometastasis) were the only statistically significant predictors of the risk of having involved nonsentinal nodes [38]. The risk of involvement of nonsentinal nodes was 22% (6/27) for patients with micrometastases versus 67% (22/33) for patients with macrometastases. Of patients with T1 primary tumors,

25% (9/36) had positive nonsentinal nodes versus 79% (19/24) for patients with larger tumors. None of the 18 patients with T1 primary tumors and micrometastases (5 of which were detected only by immunohistochemistry) had involved nonsentinal nodes versus 50% (9/18) of patients with T1 tumors and macrometastases. (The T1 tumor group was not subdivided further into T1a, T1b, and T1c subgroups, however.) For patients with tumors >2 cm, the rates of nonsentinal node involvement when there were micro- or macrometastases were 67% (6/9) and 87% (13/15), respectively.

In the multicenter validation study of Krag et al. [7], a significant correlation was found between the number of positive sentinal nodes and the chance of having positive nonsentinal nodes. When 1 sentinal node was positive, 33% (23/70) patients had positive nonsentinal nodes; when 2 sentinal nodes were positive, the nonsentinal nodes were positive in 50% (10/20) of patients; when 3 were positive, the nonsentinal nodes were positive in 60% (3/5) patients; and when ≥4 were positive, the nonsentinal nodes were positive in 83% (5/6) of patients. Similar results were found in the John Wayne Cancer Institute series [37]. Patients with 1 involved sentinal node had a 29% risk of nonsentinal node involvement versus 51% for patients with ≥2 involved sentinal nodes. This was not significant in multivariate analysis.

Other factors have not been studied as well. For example, patients with initially palpable axillary nodes also had a greater risk of involvement of nonsentinal nodes (59%) than did patients with nonpalpable axillary nodes (29%) in the John Wayne Cancer Institute series [37]. However, the influence of this factor was not analyzed in other series.

Location and Number of Involved Nonsentinal Nodes in Patients with Positive SNB

In a series from Milan, 28% of patients (24/85) with positive SNB (including those 4 patients with false-negative SNB) had positive nodes in level II or III on AxD, in addition to positive nodes in level I [17].

Patients may have a substantial number of involved nonsentinal nodes. In the series from the John Wayne Cancer Institute, 30% (16/53) of patients with positive nonsentinal nodes had 1 additional positive node, 25% (13/53) had 2, 11% (6/53) had 3, and 34% (18/53) had ≥4 [37]. In a series from Milan, 61% (20/33) of patients had only 1–2 additional positive nonsentinal nodes, but 24% (8/33) had a total of 4–10 positive nodes and 15% (5/33) had a total of 11 or more positive nodes (including the sentinal nodes) [39].

There are only very limited data on the correlates of the number of involved nonsentinal nodes. In the multicenter validation study, the number of positive nonsentinal nodes did not appear to be closely related to the number of positive sentinal nodes [7]. Patients with 1 positive sentinal node had a 26% (6/23) chance of having ≥4 positive nonsentinal nodes versus 20% (2/10) for patients with 2 positive sentinal nodes, 33% (1/3) for patients with 3 positive sentinal nodes, and 80% (4/5) for patients with ≥4 positive sentinal nodes.

It is also worth noting that (with the exception of the Milan group) these investigators did not routinely dissect nodes in axillary level III. This may result in understating the number of involved nonsentinal nodes and their locations. In a series from Jefferson Medical College, Philadelphia, when level I nodes were found to be positive, the level II nodes were involved in 41% of patients (30/73) and level III nodes in 21% (15/73) [40]. When level II nodes were involved, 31% of patients (11/35) also had metastases to level III. In two series, level III nodes were involved in 40% and 30% of patients, respectively, when level I and/or level II nodes were involved by tumor [41,42]. Nine percent of patients with 1–3 positive nodes and 47% of patients with ≥4 positive nodes had involvement of level III nodes in a series from Turin, Italy [43].

Axillary Failure Rates after a Positive SNB or Axillary Sampling without Subsequent Axillary Treatment

There are no data concerning the risk of axillary failure in breast-cancer patients after a positive SNB when further specific axillary treatment (such as completion AxD) is not performed. However, in the John Wayne Cancer Institute series of patients undergoing SNB for melanoma, there was a 33% (3/9) failure rate after a positive SNB without completion lymphadenectomy [22].

The risk of axillary failure appears to be substantial when no radiotherapy of any kind is given after a positive axillary sampling or limited axillary procedure. In the Yorkshire trial, the incidence of axillary failure in patients who had a positive axillary sampling was 12% (10/83) when AxRT was not given [25]. In a randomized trial performed between 1986 and 1990 in Nottingham, England, patients <70 years old with poorly differentiated operable breast cancers who had a positive axillary sampling (performed in conjunction with mastectomy) were randomized to receive axillary and chest-wall radiotherapy or no radiotherapy [44,45]. The trial was stopped after 77 patients had been accrued because of an interim analysis that showed a substantial benefit to the irradiated arm of the study. Axillary failure rates in the irradiated and unirradiated arms were 11% (4/36) and 41% (20/41), respectively. The rate of regional failure (not specified as to the exact nodal sites) in a similarly unirradiated patient group meeting the same eligibility criteria in a prior retrospective study was 34% (79/233), or a 10-year actuarial rate of 46% [45]. (The rate of regional recurrence in this earlier series for patients with

well or moderately differentiated tumors was 32%, or 76/239.)

In a study of patients receiving chemotherapy after modified radical mastectomy without postoperative irradiation in 4 trials of the Eastern Cooperative Oncology Group, the 10-year cumulative incidence of axillary failure in 43 patients with 1–3 positive nodes was 7% when only 2–5 axillary nodes were recovered from the specimen [46]. This rate was 12% for 18 patients with ≥4 positive nodes and 4–5 recovered nodes. In a series from the National Institute of Oncology in Budapest, Hungary, the risk of axillary failure was 8% (1/12) in patients with a positive AxD in whom ≤5 nodes were recovered when AxRT was not given versus 0 of 17 patients with failure who received AxRT [47].

Axillary Failure Rates after a Positive SNB or Axillary Sampling with Subsequent AxRT

There are no data specifically on whether AxRT and AxD are equally effective in cases of positive SNB. However, several studies of patients undergoing axillary sampling in the United Kingdom may be relevant to this issue.

As noted above, the Nottingham trial showed a reduction in the risk of axillary failure with the use of AxRT [44,45]. However, the rate of 11% in the irradiated patients was still substantial. Details of radiotherapy technique were not described. Results with AxRT after positive sampling or very limited dissection in other institutions, such as the Budapest study [47], have been better. In the Yorkshire trial, the incidence of axillary failure in patients who had a positive axillary sampling was 4% (5/123) when postoperative AxRT was given [25]. (Such treatment was not mandatory.) This result was similar to the axillary failure rate in node-positive patients initially undergoing complete AxD (without radiotherapy), which was 3% (2/75). In the Edinburgh trial, 82 of 86 patients who had positive nodes on sampling (and 1 patient in whom no nodes were identified by sampling) received postoperative AxRT, as called for in the protocol [26]. Axillary failure occurred in 7% (6/88) and 4% (3/80) of patients in the sampling and clearance groups, respectively, with positive nodes.

The Edinburgh group has also recently performed a trial comparing axillary sampling and axillary clearance in patients treated with breast-conserving surgery and radiotherapy [48,49]. AxRT was given to patients with positive nodes on axillary sampling but not to patients who underwent axillary clearance. (Details of the radiotherapy technique was not described in their reports.) With a mean follow-up of 65 months in 464 patients, the risk of axillary failure in the sampling arm of the study was 3% (8/234) versus 3% (8/232) in the clearance arm [48]. However, results were not divided according to the pathologic status of the recovered axillary nodes.

Axillary Failure Rates after a Positive SNB or Axillary Sampling with BrRT Only

Is full AxRT needed in patients who have a positive SNB, or is more limited radiotherapy sufficient? The lower portions of the axilla (level I and part but not always all of level II) are ordinarily included in the same fields used to treat the breast [31,32]. Hence, BrRT alone without specific AxRT (which includes the superior portion of levels II and III) may result in a low risk of axillary failure in patients with a positive SNB.

This concept is being tested in the American College of Surgeons Oncology Group Trial Z0011. Patients with clinical T1-2N0 tumors and a positive SNB are randomized to AxD or no specific axillary treatment, with radiotherapy explicitly restricted to the breast. The accrual goal is 1,900 patients.

There are no pilot data available from institutional studies using SNB without completion AxD as to how successful such a strategy is likely to be. There are also very few data on this topic in patients undergoing other kinds of limited axillary surgery. In a series of patients treated in Ashford, England, between 1986 and 1993 with axillary sampling and BrRT, the risk of axillary failure in patients with a positive sampling was 10% (5/50) at a mean follow-up of 61 months in the entire series [50]. Of note, an earlier report of this experience (which also included patients treated in 1994) reported an axillary failure rate of 4% (2/53) [35]. However, details of patient age, tumor size, and the use of systemic therapy were not reported in these abstracts.

Conclusions

Only limited information is available to answer the questions posed at the beginning of this section. Patients who have a positive SNB appear in general to have a substantial risk of having involved nonsentinal nodes. These additional positive nodes may be outside the standard breast tangential fields in a significant proportion of such patients. Further, patients with ≥4 positive axillary nodes are at significant risk of developing supraclavicular nodal recurrence [46,51,52]. Hence, patients with a positive SNB should generally undergo either full AxRT (including the supraclavicular nodes) or completion AxD (with selection of radiotherapy fields to be based on the pathologic findings of this procedure). On the basis of evidence from a series of patients treated with axillary sampling, these modalities are likely to be similarly effective in preventing axillary failure after a positive SNB. Selected patients with micrometastatic disease in the sentinal nodes and small primary tumors (<1–2 cm) may be at much lower risk than average of having positive nonsentinal nodes outside standard breast tangential fields. Such patients may not need full AxRT (in addition to BrRT) or undergo completion AxD (provided that

knowing the exact number of involved axillary nodes is not important in making systemic treatment decisions). However, such an approach should not be performed outside a formalized prospective study in which adequate information is given to the patient, so that she can give fully informed consent. This information must note the potentially increased risks of axillary recurrence, morbidity, and death due to breast cancer that inadequate initial axillary treatment might entail [1].

ARE AXRT AND AXD EQUALLY EFFECTIVE IN TREATING PATIENTS WITH CLINICALLY UNINVOLVED AXILLARY NODES?

Full AxRT Versus AxD

AxRT is effective in achieving control of subclinical nodal metastases, with failure rates of 1%–3% (i.e., the same range as that for AxD) [1]. Such treatment may be more effective in older than in younger patients. In a study from Beth Israel Medical Center, New York, with a median follow-up of 74 months (range = 12–246 months), the risk of axillary failure after AxRT was 8% (9/111) for patients ≤50 years old versus 2% (8/382) in older patients with nonpalpable axillary nodes [53]. (The median dose to the axilla was 50 Gy.) However, data are not available from other centers on this issue.

Is there a difference in long-term outcome between patients treated with AxD and effective AxRT? This issue has been tested in two randomized studies that used currently acceptable radiotherapy techniques and doses. The NSABP B-04 trial was conducted between 1971 and 1974 [54]. Patients with clinically uninvolved nodes were randomized to be treated with radical mastectomy (including complete AxD), total mastectomy (i.e., without AxD) plus radiotherapy to the chest wall and regional lymph nodes, or total mastectomy without radiotherapy. Adjuvant systemic therapy was not used. The axillary failure rates in the first 2 arms were very similar (1% and 3%, respectively). With an average follow-up of 125 months in all patients at last report, there was no difference in the 10-year rates of freedom from distant disease (58% and 57%, respectively) or overall survival (58% and 59%, respectively) between patients in these first two groups. (However, patients treated initially with total mastectomy alone had an axillary failure rate of 19%, and 10-year distant disease-free and overall survival rates of 55% and 54%, respectively.)

A trial conducted at the Institut Curie, Paris, between 1982 and 1987 included 658 patients treated with lumpectomy and BrRT who were randomized to receive either AxD or AxRT (plus internal mammary node irradiation) [55]. Patients with pathologically involved axillary nodes on dissection also received supraclavicular and internal mammary radiotherapy, as did all patients in both arms with central or medial lesions. The incidences of axillary recurrence were very similar in the surgical and nonsurgical groups (1% and 2%, respectively). However, with a mean follow-up of 54 months (range = 2–97 months), the 5-year distant disease-free survival rate was 97% in the surgery arm and 93% in the radiotherapy arm, which was a statistically significant difference. There was also a significant difference in overall survival rates (89% and 87%, respectively).

The reasons for the contradictory findings between these two trials are not clear. The results of the Institut Curie trial have not been updated since its initial publication; therefore, whether the results have changed with further follow-up is unknown. There were also imbalances between the two arms in the number of patients <35 years old and in the use of systemic therapy.

Another trial in this area is being conducted at the M.D. Anderson Cancer Center. Patients in a trial comparing preoperative paclitaxel to 5-fluorouracil, doxorubicin, and cyclophosphamide who are deemed appropriate candidates for breast-conserving surgery after chemotherapy are eligible for a second randomization, to undergo either a level I/II AxD or AxRT [56]. Patients with palpable nodes before chemotherapy are also eligible if the nodes disappear clinically. No results are yet available from this trial.

Is Full AxRT Necessary in the Management of the Undissected Axilla in Patients Treated with BrRT?

Full AxRT may not be needed to prevent axillary recurrence in some patients with clinically uninvolved nodes undergoing breast-conserving therapy. In the Memorial Sloan-Kettering Cancer Center series, in which a level I/II dissection was performed, 98% of histologically positive sentinal nodes were in level I, with the other 2% being Rotter nodes (which also would be in the tangential radiotherapy fields) [57]. (Data from other centers on this point have not been reported.)

Several groups have reported low axillary failure rates in selected patients (mainly elderly patients with small primary tumors) treated with BrRT without AxD. The first publication was from the Royal Marsden Hospital in Sutton, England [58]. The median follow-up in this series was 35 months (range = 3.5–98 months). The incidence of axillary failure was 5% (5/94 cases). The largest such series from the United States is from the Joint Center for Radiation Therapy [59]. There were no regional failures among 92 patients with a median follow-up of 50 months (range = 15–96 months). There were no axillary failures in a group of 21 patients treated at Washington University, St. Louis, Missouri, with a median follow-up of 51 months (range = 36–70 months) [60]. There were also no axillary recurrences in a similar series of 18 patients from Rush-Presbyterian-St Luke's Medical Center, Chicago, with a median follow-up of 60 months [61]. A

recent study from New Jersey has reported a 2% (1/43) risk of axillary failure, with a median follow-up of 76 months in the entire series [62].

Not all studies have shown such low failure rates. Sixty-five patients treated at Princess Margaret Hospital, Toronto, with BrRT but without initial AxD had a 5-year actuarial axillary failure rate of 11% at a median follow-up time of 63 months [63]. Their report did not state the correlates of axillary failure, but some patients had T2 or T3 tumors.

The time to develop a clinical axillary failure after AxRT may be prolonged [33]; hence, results with such an approach may worsen with further follow-up. For example, the risk of axillary failure was 4% (3/83) among 83 patients treated with BrRT without AxD between 1986 and 1994 in a series from Ashford, England [35]. However, a subsequent report from this group (in which patients treated in 1994 were excluded) found a failure rate of 7% (4/61) [50].

Three randomized trials have been completed that investigated the need for specific axillary treatment in patients receiving BrRT. A trial conducted in Bordeaux, France, between 1994 and 1995 included 128 patients $\geq$50 years old with T1N0 tumors [64]. Sixty-three patients were randomized to no AxD, and 65 patients underwent AxD; the rate of nodal positivity in the latter group was 26% (17/65). At 2 years, no patient in either arm had had an axillary failure.

A randomized trial was conducted in Italy between 1995 and 1998 by the Gruppo Italiano di Senologia Oncologica for 381 patients $\geq$45 years old with invasive tumors $\leq$12 mm with clinically negative axillary nodes [65,66]. (This population on the basis of data suggesting that their risk of having pathologically involved axillary nodes was approximately 10%.) Patients were randomized to receive either BrRT or radiotherapy to the breast and axilla. With a median follow-up of 26 months, 1 patient in each treatment arm had developed an axillary recurrence [65,66]. No arm edema or brachial plexopathy has occurred.

A randomized trial was performed in Naples, Italy, in which 85 patients with tumors $\leq$1.5 cm and clinically negative nodes were randomized (after breast-conserving surgery without AxD) to BrRT or BrRT plus AxRT. With short follow-up, no axillary failures were seen in either treatment arm [67]. Of note, 16% (7/45) of patients receiving AxRT developed fibrosis requiring physical therapy. Details of radiotherapy were not reported.

Another randomized trial of this issue is still in progress. The AXIL 95 trial is a multicenter French study in which 1,600 postmenopausal patients $\geq$50 years old with tumors $\leq$1 cm will be randomized to BrRT plus AxD or BrRT alone [68]. (The International Breast Cancer Study Group trial 10–93, for patients $\geq$71 years old, has a similar scheme, but BrRT is optional.)

Conclusions

Full AxRT is very effective in preventing axillary recurrence. The rate of serious complications resulting from current doses and techniques of AxRT is comparable to that of AxD [1]. However, several series have shown low nodal failure rates after BrRT without full AxRT or AxD. Patients in these studies tended to have small tumors with favorable histologic features (hence, the risk of axillary node involvement was low to begin with), were usually elderly, and often received tamoxifen. Thus, further investigation of this approach in selected patients in formalized prospective studies seems reasonable. Patients treated without AxD outside such protocols should generally receive full AxRT because the morbidity of axillary recurrence after BrRT alone could well outweigh the morbidity of properly performed AxRT.

SUMMARY

AxD must be performed if the exact number of positive axillary nodes must be known for patients with early-stage invasive breast cancer. However, for patients with clinically negative axillary nodes, achieving axillary tumor control can be accomplished in several other ways. Patients with a negative SNB treated with BrRT alone are likely to have a very low risk of axillary failure. At present, further specific treatment of the axilla is generally indicated in patients with a positive SNB. Either completion AxD or AxRT is likely to be effective in preventing recurrence in this setting. Further work is needed to delineate which patients with a positive SNB could be adequately treated with BrRT alone. AxRT is also a reasonable alternative to AxD in obtaining axillary control in clinically node-negative patients if the pathologic findings in the axilla are not used to make decisions regarding systemic therapy. BrRT is an intriguing approach for selected patients in this setting but should only be performed in well designed prospective studies.

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